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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/875,076	06/06/2001	Chen W. Liaw	AREN-0239	6379

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EXAMINER	
MERTZ, PREMA MARIA	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 10/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/875,076	LIAW ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/19/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-76 have been canceled previously and claims 102-106 have been canceled in the amendment of 9/18/2005. Previously presented claims 77-101 are under consideration.

2. Receipt of applicant's arguments and amendments filed on 9/18/2005 is acknowledged.

3. Applicant's arguments filed on 9/18/2005 have been fully considered but were non-persuasive. The issue remaining is restated below.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim rejections-35 USC § 101

5. Claims 77-101 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial utility or a well established utility.

This rejection is maintained for reasons of record set forth at pages 3-6, of the previous Office action (3/21/03) and pages 2-8 of the previous Office action (3/18/05).

The claims 77-101 are directed to an isolated polynucleotide encoding a polypeptide (hARE-2) of 373 amino acids in length. On page 8, line 4, the specification discloses that the hARE-2 protein has 53% with GPR27. The invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published on 1/5/01, 66 FR 1092.

The instant application has provided a description of an isolated nucleic acid encoding a protein, but does not disclose a specific and substantial biological role of this protein or its significance. The mere identification of the polypeptide as a GPCR is not sufficient to impart any particular utility to the claimed polynucleotide encoding the polypeptide without any information

as to the specific properties of the polypeptide. Since significant further research would be required of a person skilled in the art to determine how the claimed polynucleotide encoding the polypeptide is involved in any activities, the asserted utilities are not substantial. Furthermore, since the asserted utility is not present in a ready-to-use, real-world application, the asserted utility is not substantial.

The specification asserts the following as utilities for the claimed polynucleotide encoding a polypeptide of SEQ ID NO:20:

1. screening candidate compounds as inverse agonists, agonists or partial agonists;

2. in a research setting; and

3. disease/disorder identification and/or selection.

1. *screening candidate compounds as inverse agonists, agonists or partial agonists.*

This asserted utility is not specific or substantial. Since the same generic assays can be performed with any polynucleotide encoding a GPCR polypeptide, the asserted utility is not specific to the claimed polynucleotide encoding the polypeptide (SEQ ID NO:20) (see specification, pages 11-12). Also, since the specification does not disclose how the specific GPCR of amino acid set forth in SEQ ID NO:20 can be used, significant further research would be required of a person skilled in the art to determine how to use the claimed polynucleotide encoding the polypeptide. Since the asserted utility is not present in a ready-to-use, real-world application, the asserted utility is not substantial.

2. *in a research setting.* On page 15, lines 17-20, the specification states:

"For example, *in vitro* and *in vivo* systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and diseased, as well as understanding the role of constitutive activation as it applies to understanding the signaling cascade."

This asserted utility is not specific or substantial. Since any and all GPCRs can be used in a research setting to understand the role of the GPCR, the asserted utility is not specific. Furthermore, the specification does not disclose how this specific protein can be used, and therefore further significant research would be required by one skilled in the art to determine how to use the claimed polynucleotide encoding the protein. Since the asserted utility is not presented in a ready-to-use, real-world application, the asserted utility is not substantial.

3. *disease/disorder identification and/or selection.* This asserted utility is not specific or substantial. The specification on page 15, lines 20-23, discloses:

"The value in human orphan GPCRs is that its utility as a research tool is enhanced in that by determining the location of such receptors within the body, the GPCRS can be used to understand the role of these receptors in the human body before the endogenous ligand therefor is identified."

The specification also discloses on page 27 discloses that hARE-2 is detected in the left and right cerebellum and in the substantia. The specification discloses that the presence of a receptor at elevated concentrations in diseased tissue compared to normal tissue, can be preferably used to identify a correlation with a treatment regimen (pages 10, lines 20-23). However, the specification does not disclose any disorders that are associated with altered levels or functioning

of the claimed polynucleotide encoding the hARE-2 protein. Since the asserted utility is not presented in a ready-to-use, real-world application, the asserted utility is not substantial.

Applicants argue that they have always maintained their position that hARE-2 is a GPCR and nothing in the specification suggests that hARE-2 is anything other than a GPCR. However, contrary to Applicants arguments it is clear that the instant protein is expressed in the substantia nigra and is probably a GPCR but it is unclear from the instant specification whether the instant hARE-2 protein functions as a GPCR. As set forth in the previous Office actions, proteins can be structurally similar and yet functionally diverse. The receptors for cytokines and growth factors share structural similarity, but have diverse activities and physiological effects. For example, Murdoch et al. (2000, Blood 95:3032-3043) review chemokine receptors, which are structurally similar and yet are expressed on different cell types and bind different ligands such that the receptor response is highly variable (p. 3032, Abstract). Ji et al. (1998, Journal of Biological Chemistry 273:17299-17302) review the functional diversity among the structurally related G protein-coupled receptors.

Applicants argue that they have provided an alignment of hARE-2 with GPR27 as Figure 1 of priority provisional application US 60/136,436 and that homology between hARE-2 and GPR27 is observed over the entire length of hARE-2. However, contrary to Applicants arguments, the issue here is not that hARE-2 is a GPCR but that an analysis of the instant specification does not meet the requirements of 35 USC 101 for a specific and substantial asserted utility or a well-established utility. Graph 1 (9/19/03) has been provided to establish a specific and substantial utility for hARE-2. An asserted utility must meet the three-pronged test

of being credible, specific and substantial. The utilities for the proteins recited in the instant specification are generic utilities that fail to satisfy all three prongs. In the instant case, GPCRs are structurally similar compounds with diverse functions. The skilled artisan would have to conduct significant further research to determine the particular functions of the hARE-2 protein in order to identify a specific and substantial utility for this new hARE-2 protein. Therefore, the asserted utilities in the instant specification are not specific or substantial.

Applicants argue that the skilled artisan would appreciate from Graph 1 that, e.g. an inverse agonist or an antagonist of hARE-2 would promote the viability of neurons of the substantia nigra and therefore be useful in Parkinson's disease. However, contrary to Applicants arguments, there is no doubt that hARE-2 reduces the level of intracellular cAMP. However, the specification as originally filed merely discloses that hARE-2 is present in substantia nigra. It would have taken significant research to determine the role of hARE-2 in substantia nigra and the role of hARE-2 in a disease such as Parkinson's disease and only once these roles were determined, then hARE-2 could be used to screen for compounds to treat the disease. Therefore, one of skill in the art, as of the filing of the instant application, would not have discerned the role of hARE-2, because there is no disclosure suggesting what type of role is played by hARE-2.

The utility is neither specific nor substantial

Applicants argue that the disorders to be treated are specific diseases related to the substantia nigra, such as motor impairment disorders, including Parkinson's disease. However, this argument has been fully considered but is not persuasive, because the specification only discloses that hARE-2 is present in the substantia nigra, and right and left cerebellum (page 27,

Table C). The credibility of any general utility asserted in the instant specification is not being questioned. The assertion that GPCRs can be used to screen for candidate compounds (pages 11-12 of the specification) is not a specific assertion of utility. Also, the specification does not state what the role of hARE-2 is and what types of functions or disorders hARE-2 is involved in. The specification provides no nexus between hARE-2 expression and any specific disease or a change in expression of hARE-2 with any specific disease. Since significant further research would be required before hARE-2 could be used, the asserted utility is not substantial.

Applicants argue that the specification does not blindly recite the use of hARE-2 for treating unknown diseases or disorders. Applicants are absolutely right. The specification fails to provide any disclosure that hARE-2 can be used to treat disorders associated with the substantia nigra, such as motor impairment disorders. The disclosure of the instant specification fails to provide the skilled artisan with an identifiable benefit or a minimal utility. What can the skilled artisan do with a protein armed only with the assertion that it is expressed in the substantia nigra? The specification provides no clear nexus between any particular disease state and any specific change in hARE-2 form or quantity, and thus it is up to the skilled artisan to determine such empirical experimentation. Since further research would be required before hARE-2 could be used in a "real world" treatment of a specific disease, the asserted utility is not substantial.

Applicants argue that the Office has the burden to provide evidence showing that the utility is not credible and that the Revised Interim Utility Guidelines Training Material (herein after "Training Material") states that "an assay method for identifying compounds that themselves have a 'substantial utility' define a 'real world' context of use." See page 6 of the

Training Material. However, contrary to Applicants assertion, there is no issue with the credibility of the asserted utility. The issue is that the assertion that hARE-2 can be used in an assay to identify "possible" ligands for treating a disorder of the substantia nigra (such as Parkinson's disease) is not specific or substantial. The specification only asserts non-specific roles of GPCRs. If the specification had asserted that hARE-2 is up-regulated in Parkinson's disease, then the assertion of utility would have been specific. Unfortunately, such a disclosure is not in the specification as originally filed.

The specification merely states that hARE-2 is expressed in the substantia nigra. It does not characterize the role of hARE-2 in the substantia nigra. Therefore, the skilled artisan would have to conduct further experiments to determine the role of hARE-2 in the substantia nigra. Is hARE-2 up-regulated or down-regulated in Parkinson's disease? Without this information, the skilled artisan would not know if it was desirable to identify drugs that agonize or antagonize hARE-2 as treatment for disorders of the substantia nigra. Thus the specifications assertion that hARE-2 is a GPCR is credible and this credibility has never been questioned but the assertion of hARE-2's role in disorders of substantia nigra is not specific or substantial.

In conclusion, the specification fails to provide an assertion of a specific and substantial utility for the claimed nucleic acid encoding hARE-2 and there is no well-established utility of the hARE-2 protein since the GPCR family is known for its diversity.

Claim rejections-35 USC § 112, first paragraph

6. Claims 77-101 are also rejected under 35 U.S.C. 112, first paragraph.

This rejection is maintained for reasons of record set forth at pages 3-6, of the previous Office action (3/21/03) and pages 2-8 of the previous Office action (3/18/05).

Specifically, since the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

No claim is allowed.

Claims 77-101 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (571) 272-0829.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Prema Mertz

Prema Mertz Ph.D.
Primary Examiner
Art Unit 1646
September 28, 2005